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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/621,897	07/20/2000	Richard W. Scott	CEPH-1066	4645

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EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	15

DATE MAILED: 06/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/621,897	Applicant(s) Scott
	Examiner Dave Nguyen	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 10, 2003* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *39-42, 44, 46-64, and 77-98* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *39-42, 47-64, and 77-98* is/are rejected.

7) ☒ Claim(s) *44 and 46* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claims 39, 40, 44, 46, 82, and 88 have been amended by the amendment filed March 10, 2003.

Claims 39-42, 44, 46-64 and 77-98, to which the following ground of rejection is applicable, are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-42, 47-64 and 77-98 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A gene-targeted mouse heterozygous for a human Familial Alzheimer's Disease (FAD) mutation comprising a human mutation of the preselinin-1 (PS-1 gene) and a human transgene for Swedish APP695, wherein the A.beta.42 protein level is elevated relative to the A.beta.42 protein level in a wild-type mouse.

does not reasonably provide enablement for any other claimed embodiment embracing any other non-human transgenic non-human mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claimed invention is directed to a gene-targeted rodent (a knock-in rodent, wherein a particular endogenous gene is targeted for replacement by homologous recombination, *e.g.,* homologously targeted for accepting a DNA sequence encoding a functionally active PS-1 protein comprising any mutation as listed in claim 97, and a DNA sequence encoding a human APP polypeptide having the Swedish APP695 mutation, which targeted rodent is still a transgenic mouse) heterozygous or homozygous for FAD PS-1 mutation comprising a human p264L mutation and for the Swedish APP695 mutation, or a method for screening chemical compounds for the ability to decrease *in vivo* level of A-beta42 peptide, obtaining a tissue sample from said mouse, *e.g.,* brain tissue, non-brain tissue, and body fluids, and measuring the relative amount of A-beta42 peptide in the tissue sample.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The newly amended claims are readable on any gene-targeted non-human rodent heterozygous or homozygous for human Familial Alzheimer's disease (AD). The specification contemplated that the claimed gene-targeted rodent for any presenilin-1 (PS-1) mutation and Swedish mutation either exhibits the pathology and symptomatology of ADA, or can be used in a screening assay to screen for *in vivo* inhibitors and for discovering and testing the efficacy and suitability of putative chemicals compounds for their ability to inhibit the formation of Aβ42 peptides in the brain tissues, other tissues, and body fluids. However, the specification does not provide sufficient guidance and/or evidence to reasonable enable any rodent other than the claimed mouse (rabbit, for example). While the state of the art of transgenics is such that one skilled in the art can deliver and express a gene in a desired animal, it is not reasonably predictable for one skilled in the art to produce any transgenic mammal other than the exemplified mouse that exhibit a desired phenotype, regardless whether a gene targeted modification technique rather than a traditional introduction

of a desired exogenous protein encoded construct into embryonic cells. Applicants contemplates that by targeting any DNA vector construct encoding any mutant PS-1 gene product (human PS1 mutant cDNA as listed in claim 97, for example) or a human APP polypeptide comprising the Swedish mutation via homologous recombination into an endogenous genomic site containing the endogenous PS1 gene of any murine cell including murine pluripotent, murine embryo-derived stem (ES) cells, an genetically modified ES cell, for example, can be produced and can be employed to produce a knock-in non-human mammal comprising germ-line chimera as the result of fusion between the genetically modified ES cell and the mouse embryos (page 10). The specification further provides working examples showing the making by ES technology and cross-breeding of a gene-targeted mouse heterozygous for human presenilin-1 (PS-1) mutation and Swedish mutation, said mouse comprising, in its genome, a DNA sequence encoding a functionally active PS-1 protein comprising the human P264L mutation and a DNA sequence encoding a human APP polypeptide having the Swedish APP695 mutation, wherein the A.beta.42 protein level is elevated relative to the A.beta.42 protein level in a wild-type mouse. However, it is not apparent how such guidance and/or working examples can be reasonably extrapolated to any claimed rodent other than the exemplified mouse, particularly on the basis of applicant's disclosure and the doubts expressed in the art of record. At the time the invention was made, the art of transgenics including gene targeted modification using ES cell technology was known to be unpredictable with respect to the efficacy of incorporation of transgene, levels of expression as a result of the incorporation, and the phenotypes expressed as a result of the transgene incorporation via homologous recombination in ES cells. Palmiter *et al.* (PNAS, 1991) teach that directed expression of any gene to any specific cell type of an animal by using established transgenic methodology is theoretically possible by combining the regulatory regions(s) of a gene that is expressed in a cell-specific manner with any mRNA-encoding structural gene. Palmiter *et al.,* note, however, that not all gene constructs work well; the two most common problems are inappropriate expression patterns and failure to achieve adequate expression levels (page 478, left column, first paragraph). Wall (Theriogenology, 1996) discloses the unpredictability of transgene behavior due to factors such as unidentified control elements (during the fusion between ES cell and murine embryos) and may result in

variable expression. Whitelaw *et al.* (Transgenic Research , 1991, page 10, column 1 bridging column 2) indicates that exogenous DNA. constructs, intronless constructs or constructs containing the introns, do affect variation in gene expression. Palmiter (Ann Rev. Genes, 20, p. 465-498) indicates that variable or inappropriate expressions do often occur in transgenic founder animal and/or offspring (pages 482 and 483).

More specifically as to the lack of reasonable correlation between rodent and other species in ES technology, Polejaeva *et al.* (Theriogenology, Vol. 53, pages 117-126, 2000), states:

> Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. The most profound is that DNA can only be added, not deleted, or modified in situ. Also, the integration of foreign DNA is random; this could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's health. Finally, transgenic animals generated using pro-nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. Therefore, the production of the required phenotype coupled to germ line transmission could undue experimentation. See page 119.

In addition, the prior art and post-filing art replete with references, which indicate that ES technology, is generally limited to the mouse system, at present and that only "putative" ES cells exist for other species. See Rulicke et al. (Experimental Physiology, Vol. 85, 2000, page 2092), who supports this observation. Rulicke *et al.* disclose, "The ES cell technique, although of great interest in other model organisms and in livestock species, has been successfully used only in mouse so far." Furthermore, the state of the art for chromosomal insertion of DNA into a genetically modified animal as exemplified by Bishop (Heprod. Nutr. Dev, 1998, Vol. 36, pages 607-618) teaches that:

> The preferred route to an altered genome is recombination between a transgene and homologous resident DNA in totipotent ES cells followed by introduction of the engineered cells into the inner cell mass of host blastocysts and germline transmission from the resulting chimera. To date, this approach is available only in mice, because despite a considerable effort, ES cell lines with suitable properties have not been established in other species. See page 608.

As the claims encompass a transgenic rodent comprising modified ES cells by using any technology, and the as-filed specification fails to teach the establishment of true ES cells for use in the production of any transgenic rodent than the exemplified mouse, the state of the art supports that only

rodent ES cells were enabled for used in the production of transgenic rodent. Taken together, the current status of transgenic art is such that generating transgenic non-human mouse with a requisite phenotype, *e.g.,* FAD, is neither routine nor predictable, unless proven by a working example, let alone a claim that embraces any transgenic non-human mammal other than rodent as claimed. It is apparent that neither the as-filed application nor any of the prior art of record provides any evidentiary support so as to reasonably extrapolate from the exemplified mouse to the full breadth of the claimed invention as presently claimed. As such, a skilled artisan would not accept the making and use of any claimed rodent is reasonably predictive at the time the invention was made.

The data presented in the as-filed specification support a conclusion of unpredictability and lack of reproducibility. This conclusion coupled with state of the art is consistent with a finding of lack of enablement for the practice of what is claimed. Thus, based upon the evidence in the record, which demonstrates that there is a reasonable basis for questioning the assertions regarding the enablement of the claimed invention, the present claims are properly rejected under 35 U.S.C. 112, first paragraph.

To the extent that applicant's response (pages 10-13) is relevant to the stated rejection, the response has been considered but is not found persuasive because of the following reasons:

Applicant again asserts that applicant does not employ a transgenic technology, however, an *in vivo* gene targeting technology wherein an exogenous gene is intergrated in order to remove a target gene by homologous recombination is the same as transgenic technology, which essentially requires techniques that enables a person skilled in the art to make a transgenic rodent that exhibit a phenotypic change as the result of a permanent integration of a transgene at a desired target site in the chromosomal DNA of the rodent. Applicant further asserts on page 12 that due to targeted homologous recombination, the position effect as described in the prior art is avoided. In response, the examiner maintains that there is no evidence from any prior art of record or the as-filed specification to demonstrate a reasonable extrapolation from the exemplified mouse to a generic rodent as claimed. The fact that homologous recombination can done in a mouse as shown in the as-filed specification and the prior art does not necessarily lend any evidentiary

support to show that gene targeted technology can be employed in a non-murine rodent with routine experimentation such that a position effect can be avoided and applicant's phenotypic change can be exhibited. As such, showtcomings of trasngenic technology, including variable expression as described in the prior art of record remain deemed relevant to the claimed invention. Furthermore, and in addition to the position effect, Wall (Theriogenology, 1996) discloses the unpredictability of transgene behavior due to factors such as unidentified control elements (during the fusion between ES cell and murine embryos) and may result in variable expression. Whitelaw *et al.* (Transgenic Research , 1991, page 10, column 1 bridging column 2) indicates that exogenous DNA. constructs, intronless constructs or constructs containing the introns, do affect variation in gene expression. Palmiter (Ann Rev. Genes, 20, p. 465-498) indicates that variable or inappropriate expressions do often occur in transgenic founder animal and/or offspring (pages 482 and 483).

More specifically as to the lack of reasonable correlation between rodent and other species in ES technology, Polejaeva *et al.* (Theriogenology, Vol. 53, pages 117-126, 2000), states:

> Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. The most profound is that DNA can only be added, not deleted, or modified in situ...Finally, transgenic animals generated using pro-nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. Therefore, the production of the required phenotype coupled to germ line transmission could be undue experimentation. See page 119.

In addition, the prior art and post-filing art replete with references, which indicate that ES technology, is generally limited to the mouse system, at present and that only "putative" ES cells exist for other species. See Rulicke et al. (Experimental Physiology, Vol. 85, 2000, page 2092), who supports this observation. Rulicke *et al.* disclose, "The ES cell technique, although of great interest in other model organisms and in livestock species, has been successfully used only in mouse so far." Furthermore, the state of the art for chromosomal insertion of DNA into a genetically modified animal as exemplified by Bishop (Heprod. Nutr. Dev, 1998, Vol. 36, pages 607-618) teaches that:

> The preferred route to an altered genome is recombination between a transgene and homologous resident DNA in totipotent ES cells followed by introduction of the engineered cells into the inner cell mass of host blastocysts and germline transmission from the resulting chimera. To date, this

approach is available only in mice, because despite a considerable effort, ES cell lines with suitable properties have not been established in other species. See page 608.

Applicant further asserts that ES technology is available and that hamster ES cells, rat ES cells are available in the prior art, which includes Thompson *et al.,* Doetschman and Iannaccone. In response the examiner maintains that as of 1996, no germline-competent rat ES cells lines exist despite the fact that ES cells from rats are available in the prior art (see Loring, Neurobiology of Aging, Vol. 17, No. 2, pp. 173-182, 1996, particularly page 182, column 2, last full paragraph). In fact and to further rebut applicant's response with regard to the issue of the lack of reasonable predictability in the making and use of a transgenic rat model for Alzheimer's Disease, Ganten (Biomedical and Health Res., 23 (human genome Analysis), 450-457, 1998) and Ardis (abstract view, Society for Neuroscience Abstracts, 2001, vol. 27, no. 2, pp. 2344) that even in 1998 leading to 2001, while transgenic rats can be made to carry some transgenic DNA in their offsprings, the phenotype of all positive animals was negative and abnormalities with respect to behaviour was suggested so far (page 453, last full paragraph). As such, the examiner maintains that at the time the invention was made, one of skill in the art would have required an undue experimentation to reasonably extrapolate from the making and use of the claimed murine mode to the making and use of any other rodent model as broadly claimed.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 39-42, 44, 46-64, 77-98 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,284,924 taken with Duff *et al.* (US Pat No. 5,898,094), and claims 1-4 of US Pat No. 5,850,003. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims embrace a gene-targeted mouse heterozygous for human presenilin-1 (PS-1) mutation and Swedish mutation, said mouse comprising, in its genome, a DNA sequence encoding a functionally active PS-1 protein comprising the human P264L mutation and a DNA sequence encoding a human APP polypeptide having the Swedish APP695 mutation, wherein the A.beta.42 protein level is elevated relative to the A.beta.42 protein level in a wild-type rodent. While the claims of the '924 patent does not explicitly claim the Swedish mutation in the transgenic mice, it would have been obvious for one of ordinary skill in the art to have made or added the Swedish mutation to the mice of the of the '924 patent so as to enhance or induce abnormal neuropathology which includes an elevated level of Aβ peptides in the brain of mice, as taught in Duff (Claims, columns 5, 6, and 9-11, particularly column 7) and the '003 patent *e.g.,* columns 12, 15, 16, 23, 24.

Thus, the claims are obvious variants of one another.

A filing of a proper TD would obviate the rejection as acknowledged by applicant on page 16 of the response.

Claims 44 and 46 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

THIS ACTION IS MADE FINAL. See MPEP § 609(B)(2)(i). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Dianiece Jacobs, whose telephone number is **(703) 305-3388.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Trong Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER